Res 2:465-8 in view of Datta et al. (1997) *Cell* 91:231-41, under the reasoning of Paper No. 13, pages 4-5, and Paper No. 16. Claim 5 is objected to as dependent upon a rejected base claim.

2. Status of Previous Final Office Action (Paper No. 21)

Applicant gratefully acknowledges the Examiner's decision to vacate the previous final Office Action (Paper No. 21).

3. Rejection Under 35 U.S.C. § 103(a)

The Examiner has indicated that claims 1-4 remain rejected under 35 U.S.C. § 103(a) as unpatentable over Cuevas et al. (1997) *Eur J Med Res* 2:465-8 in view of Datta et al. (1997) *Cell* 91:231-41, under the reasoning of Paper No. 13, pages 4-5, and Paper No. 16. As discussed in the telephone interview on November 8, 2002, Applicant respectfully disagrees with the rejection and requests the Examiner to withdraw the rejection for the following reasons.

Applicant respectfully submits that the Examiner has failed to make a prima facie case for an obviousness rejection because the rejection rests on a number of assumptions, any one of which if incorrect would overcome the rejection: (1) for any given apoptosis inhibitor, one cell type can be substituted for another, i.e., cells are all alike; (2) for any given cell type, one apoptosis inhibitor can be substituted for another, i.e., apoptosis inhibitors are all alike; and (3) apoptosis is a single entity, regardless of the type of underlying stress. Applicant respectfully submits that not one of these propositions is sustainable. Applicant therefore respectfully requests the Examiner to withdraw the rejection.

Cells are not all alike.

At a minimum, it goes almost without saying that the first proposition is untenable because it is widely appreciated that differentiated cells from various tissues are structurally and functionally dissimilar. Because neurons and cardiac myocytes are so plainly distinct in their structure and function, the rejection, which seeks to rest on the proposition that Akt, an apoptosis inhibitor reported to be effective in neurons, is to be expected to be effective in cardiac myocytes, is nonsustainable on its face.

Apoptosis inhibitors are not all alike.

Even among growth factors thought to be survival factors, e.g., apoptosis inhibitors, it also goes almost without saying that one apoptosis inhibitor cannot arbitrarily be substituted for another. For example, growth factors for the most part act through specific cell surface receptors. Platelet-derived growth factor (PDGF), nerve growth factor (NGF), and insulin-like growth factor-1 (IGF-1) each have their own specific receptors. Thus while neurons expressing NGF receptor may be responsive to NGF, other cell types not expressing NGF receptor would not be expected to be responsive to NGF. Conversely, cells expressing PDGF, NGF, and IGF-1 may not be responsive to another growth factor for which there is little or no expression of receptors specific for that growth factor. It is therefore untenable to suppose that for any given cell type, one apoptosis inhibitor can arbitrarily be substituted for another.

It is to be noted that Applicant does not mean to suggest by this argument that Akt is a growth factor. Indeed, Akt, unlike the foregoing growth factors, is an intracellular molecule.

Apoptosis is not a single entity.

There are many reports in the literature of Akt-independent cellular survival, showing that not all apoptotic or anti-apoptotic stimuli funnel through this regulatory pathway. Furthermore, it is clear that there are diverse intracellular mechanisms that promote cell death. In the broadest sense, in apoptosis there is an "intrinsic" cell death pathway and an "extrinsic" cell death pathway. The intrinsic pathway functions through the mitochondria and is largely sensitive to Akt. In contrast, the extrinsic pathway involves Fas ligand and caspase 8, and is largely insensitive to Akt. In addition, caspase-independent apoptosis is also understood at this time. This latter process involves AIF (apoptosis-inducing factor), but apparently not Akt. Therefore methods directed to protecting against apoptosis are expected to be heterogeneous because it appears that apoptosis itself is heterogeneous in nature.

Further in this regard, it is not at all obvious or expected that apoptosis induced by growth factor withdrawal, cell-cycle discordance, loss of cell adhesion, or DNA damage should be the same as apoptosis induced by acute ischemia/reperfusion.

Claims 1, 4 and 5 are directed to a method for treating myocardial infarction involving administering to a subject in need of such treatment an Akt molecule in an amount effective to inhibit cardiac tissue necrosis in the subject. Claims 2 and 3 add the limitation that the cardiac

tissue necrosis is mediated by increased apoptotic cell death of specific cell types in cardiac tissue.

Cuevas teaches simply that one particular growth factor, FGF, promotes survival of cardiomyocytes under conditions of acute ischemia/reperfusion. The Examiner acknowledges that "Cuevas et al. do not include an Akt molecule in the treatment protocol." Paper 13, page 5. Importantly, FGF does not activate Akt in cardiomyocytes, skeletal myocytes, or vascular endothelial cells. This point was discussed at length during the telephone interview with the Examiner on November 8, 2002. Additionally, as pointed out above, there are many reports in the literature of Akt-independent cellular survival, showing that not all apoptotic or anti-apoptotic stimuli funnel through Akt. Therefore the observation in Cuevas that FGF promotes cardiomyocyte survival says nothing about the role or potential role of Akt in promoting the survival of cardiac tissue as claimed.

Applicant respectfully submits that the teachings of Datta do not provide what is missing from the Cuevas reference, because Datta does not teach that Akt is an inhibitor of apoptosis in cardiac tissue. There thus exists no motivation to combine Cuevas and Datta because they do not provide a suggestion or motivation to combine the references in order to arrive at the claimed invention.

The observation that Akt suppresses apoptotic death in lymphoid, neuronal, and epithelial cells does not reasonably suggest that Akt is expected to be an inhibitor of apoptosis in cardiac tissue. The Examiner cited Datta for the proposition that Akt is an inhibitor of apoptosis in a variety of cell types. While the passage on page 231, 2nd column of Datta cited by the Examiner points to a number of references, none of those references teaches that Akt is an inhibitor of apoptosis in cardiomyocytes, skeletal myocytes, or vascular endothelial cells. Indeed, the pertinent citations in Datta deal with the following cell types: BAF/3 (IL-3-dependent lymphoid cell line) and 2780a (IL-2-dependent T cell line) (Ahmed et al.); neurons (Dudek et al.); fibroblasts (Kauffman-Zeh et al., Kennedy et al., and Kulik et al.); and epithelial cells (Khwaja et al.). The Datta reference itself teaches that Akt promotes cell survival in neurons, under conditions of growth factor withdrawal. In view of the fact that differentiated cells from various tissues are widely recognized to be structurally and functionally dissimilar, the observation that Akt suppresses apoptotic death in lymphoid cells, neurons, fibroblasts, and epithelial cells does not reasonably suggest to one of skill in the art that Akt is expected to be an inhibitor of

apoptosis in cardiac tissue. Thus Datta does not teach or reasonably suggest that Akt is an inhibitor of apoptosis in cardiomyocytes, skeletal myocytes, or vascular endothelial cells, under any conditions (either growth factor withdrawal or acute ischemia/reperfusion).

Datta also teaches that certain growth factors, other than FGF, induce activation of Akt, which in turn phosphorylates and thus inactivates BAD, a promoter of cell death. The growth factors examined in Datta include PDGF, NGF, and IGF-1. Notably, the growth factors examined in Datta do not include FGF, the growth factor disclosed in the Cuevas reference. As discussed at some length in the telephone interview with the Examiner, FGF is an example of a growth factor that does not activate Akt in cardiomyocytes, skeletal myocytes, or vascular endothelial cells.

Datta goes on to note that the PI3'K-Akt-BAD pathway is not the only survival pathway used by cells (see page 236, 2nd column, lines 16-17; page 237, 2nd column, lines 6-7; page 238, Figure 8 and 2nd column). Indeed, Datta suggests that there exist survival pathways that bypass Akt altogether (page 238, Figure 8 and column 2). Therefore, the fact that a particular growth factor is observed to promote cell survival in one type of cell may not predictably have any bearing on the role or potential role of Akt in that cell type. In particular, the fact that FGF may be observed to promote cell survival in one type of cell does not predictably have any bearing on the role or potential role of Akt in that cell type.

4. Summary

Applicants respectfully submit that the Examiner has not made a prima facie case for an obviousness rejection based on Cuevas et al. in view of Datta et al., and the rejection accordingly should be withdrawn. Cuevas, in addition to making no teaching with respect to Akt, teaches only that FGF, a growth factor that does not activate Akt in cardiomyocytes, skeletal myocytes, or vascular endothelial cells, promotes survival of cardiomyocytes. Datta teaches only that (1) certain growth factors other than FGF, acting through Akt, promote survival of certain cell types other than those of interest in the instant invention, and (2) there exist other survival pathways that bypass Akt. For the reasons given above, Applicant respectfully submits that there is no suggestion, teaching, or motivation to combine the references as suggested by the Examiner, and furthermore there is no reasonable expectation of success even if they were combined. If one cannot discern in the rejection any finding that there was a suggestion, teaching, or motivation to combine the prior art references cited against the pending claims, the conclusion of obviousness

as a matter of law cannot stand. Therefore the Applicant respectfully requests the Examiner to withdraw the rejection of claims 1-4 under 35 U.S.C. § 103(a), and thus also the objection to claim 5.

Applicant believes that each of the pending claims now is in condition for allowance. Applicant respectfully requests that the Examiner telephone the undersigned attorney in the event that the claims are not found to be in condition for allowance.

If the Examiner has any questions or believes that a telephone conference with Applicant's attorney would prove helpful in expediting the prosecution of this application, the Examiner is urged to call the undersigned at (617) 720-3500 (extension 257).

Respectfully submitted,

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